

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Robin ROBINSON *et al.* Confirmation No.: 5752

Serial No.: 10/617,569 Art Unit No.: 1648

Filed: July 11, 2003 Examiner: Myron G. Hill

FOR: FUNCTIONAL INFLUENZA VIRUS-LIKE PARTICLES (VLPs)

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

In response to the Final Office Action of January 27, 2009, Applicants respectfully request a review of the above-identified application prior to the filing of an Appeal Brief. A Notice of Appeal is filed herewith under 37 C.F.R. §41.31. Applicants submit that the rejections of record are clearly improper and request that the rejections be withdrawn.

Claims 34-65 remain pending in the application. Claims 34-55 and 64-65 are directed generally to virus-like particles (VLPs) comprising avian influenza HA, NA, and M1 proteins. Claims 56-63 are directed generally to a purified VLP comprising an avian influenza M1 protein. Reconsideration of claims 34-65 in light of the remarks below is respectfully requested.

Obviousness Rejections Under 35 U.S.C. 103(a)

The Examiner has rejected claims 34-65 under 35 U.S.C. § 103(a) as obvious over Latham *et al.* (*J. of Virology*, 2001, 75: 6154-6165) in view of Saito *et al.* (*Vaccine*, 2001, 20: 125-133). Specifically, the Examiner asserts that Latham *et al.* disclose VLPs comprising human influenza HA, NA, M1, and M2 proteins, but acknowledges that Latham *et al.* do not teach VLPs comprising avian influenza proteins, including avian M1. Saito *et al.*, according to the Examiner, do not teach VLPs, but do disclose the avian influenza strain H9N2. Based upon the disclosures of these two references, the Examiner alleges that one of ordinary skill in the art would have been motivated to make the claimed avian influenza VLPs using the teachings of Latham *et al.* in combination with the avian proteins disclosed by Saito *et al.* Applicants respectfully submit this rejection is clearly erroneous for two important reasons.

No Teaching, Suggestion, or Motivation in the Prior Art to Use Avian M1 for VLP Production:

First, Applicants respectfully submit that the prior art provides no teaching, suggestion, or motivation for the use of an avian influenza M1 protein as specified in independent claims 34 and 56 to produce VLPs (both claims specifically require an avian M1 protein). Instead of the teaching a VLP comprising an avian influenza M1 protein, the prior art teaches the use of the human influenza M1 protein to produce VLPs (see the M1 protein of human influenza strain A/Udm/72 as disclosed by Latham *et al.*). Specifically, Latham *et al.* teach that the human influenza M1 protein “plays a central role in virus assembly and release.” See Latham, page 6164, column 1. Based upon on the teachings of Latham *et al.*, one of ordinary skill in the art would not have been motivated to use an avian influenza M1 protein to produce VLPs. Rather, one of skill in the art would have used the human influenza M1 protein, which was taught by Latham *et al.* to be important for virus assembly and release.

Furthermore, the skilled artisan would not have been motivated to deviate away from using Latham’s human influenza M1 protein because the skilled artisan recognizes that M1 confers no relevant immunogenicity. Rather than M1, the skilled artisan understands that the influenza proteins HA and NA are the primary antigens leading to the formation of protective immunity against influenza. Thus, the skilled artisan would have been motivated to use the human influenza M1 protein of Latham *et al.* (and not the avian M1 of the present invention) in combination with various HA and NA proteins, such as those seen in pandemic strains, for producing VLPs. This reasoning is consistent with the disclosure of Latham *et al.*, which states “[t]his novel approach for the assembly of virus particles has great potential for the design of vaccines against new influenza virus variants...even extremely dangerous subtype antigen combinations, such as H1N1 (from the 1918 Spanish flu) or an HA-NA combination with pandemic potential, could be incorporated into VLPs...” See Latham, page 6164, col. 1 (emphasis added). The deficiencies of Latham *et al.* are not cured by Saito *et al.*, which provides no teaching or suggestion for using of an avian protein, much less an avian M1 protein, for VLP production.

Although the criteria for finding obviousness was made more flexible by *KSR*, the Court still recognizes an Examiner must establish “an apparent reason to combine...known elements.” *KSR Int’l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-41. Moreover, “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning...to support the legal conclusion of obviousness.” *Id.*, citing *In re Kahn*, 441 F.3d 977, 988 (emphasis added). Applicants respectfully submit the Examiner has not met this burden. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness based upon the cited references and therefore the rejections must be withdrawn.

Surprising and Unexpected Properties Conferred to VLPs using Avian M1:

As shown above, the Examiner has attempted to establish a *prima facie* case of obviousness using Latham *et al.* in view of Saito *et al.* In a situation where the Examiner establishes a *prima facie* case of obviousness, which as shown above he has not, the burden then shifts to the Applicant to show evidence of nonobviousness. As stated in the MPEP at 716.02(a),

Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. (emphasis added).

To rebut the purported *prima facie* case of obviousness, Applicants have shown that the VLPs of the present invention have unexpected and surprising properties as compared to the prior art VLPs. Specifically, Applicants' response filed September 12, 2008 included a Declaration (the "Smith Declaration") that provided data demonstrating that VLPs comprising avian influenza M1 proteins form much more efficiently than the prior art VLPs which were comprised of human influenza M1 proteins. In the declaration, Applicants have shown that a structural feature found only in the avian influenza M1 protein (a "YKKL" L-domain at amino acid positions 100-103 of M1) is vital to the formation of VLPs and results in the unexpected property of markedly increased VLP formation. Accordingly, Applicants have shown the presence of an unexpected property to support a finding of non-obviousness. As the MPEP at 716.02(a) states, "the presence of a property not possessed by the prior art is evidence of nonobviousness." (emphasis added).

At page 3 of the Office Action, the Examiner argues that the claims are drawn to a product, not a method of making a product. Applicants agree that the claims are drawn to a product, but dispute the Examiner's inference that the surprising properties are not applicable to the present claims because the claims are not methods. The unexpected properties shown by the Applicants are an absolutely critical feature of the claimed VLPs. Specifically, the unexpected property possessed by the VLPs is driven by the avian influenza M1 protein, which is part of the claimed product. The claimed VLPs possess a structural feature (the YKKL L-domain of avian M1) that results in the unexpected property of significantly increasing the level of VLPs obtained from cultured cells. Applicants submit that the ability to assemble correctly and efficiently is a necessary and integral property of a VLP. Simply stated, the Examiner is asserting that a showing of surprising efficacy for the claimed VLPs is the only evidence Applicants can use to rebut the purported *prima facie* case of obviousness, which is plainly contrary to the MPEP:

"Evidence that a compound is unexpectedly superior in one of a spectrum of common properties...can be enough to rebut a *prima facie* case of obviousness. No set number of examples of

superiority is required.” MPEP 716.02(a), citing *In re Chapp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). (emphasis added)

As the MPEP specifies at 716.02(e), “evidence of unexpected results must compare the claimed invention with the closest prior art...” (emphasis added). Applicants submit that they have met this burden. Specifically, the Smith Declaration compares the claimed invention with the closest prior art, namely the Latham *et al.* reference. In doing so, Applicants have shown that only avian influenza virus strains contain the sequence “YKKL” at amino acids 100-103 of the avian influenza M1 protein. In contrast, human influenza strains, including the human seasonal strain A/Udm/72 as disclosed by Latham *et al.*, contain a defective “YRKL” L-domain in M1. The Smith declaration shows a dramatic difference in VLP formation between YKKL containing avian strains such as A/Hong Kong/1073/99 (disclosed in the present application) compared to the YRKL containing human strain of Latham *et al.* (A/Udm/72), and provides data demonstrating that the amino acid mutation in the L-domain is essential to the surprising feature.

In addition, Applicants acknowledge they have the burden of establishing that the results are “unexpected and significant.” MPEP 716.02(b) (emphasis added). Moreover, Applicants understand “the evidence relied upon should establish ‘that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance.’ MPEP 716.02(b), citing *Ex Parte Gelles*, 22 USPQ2d 1318 (BPAI 1992) (emphasis added). To this end, Applicants have shown that use of the seasonal human M1 of Latham *et al.* produces a mere fraction of the VLPs as compared to when avian M1 proteins are used, such as those disclosed in the present application (see Smith Declaration at paragraph 8b, which shows that the YRKL L-domain containing Udm M1 of Latham *et al.* yields only 12% of the level of that produced by the YKKL L-domain containing avian M1). Applicants respectfully submit that this difference is clearly statistically significant.

Furthermore, Applicants submit that such a statistically significant unexpected result is also of enormous practical significance. The increased formation and recovery of VLPs with avian M1 is critical to vaccine development. Using a human seasonal M1 protein such as the one disclosed by Latham *et al.* does not produce sufficient quantities of VLPs for use in a vaccine. As shown by the Smith Declaration, the only way to generate recoverable amounts of VLPs necessary for vaccine production is through the use of an avian derived M1 protein, such as the one disclosed in the present application and presently claimed.

In addition, Applicants submit that the Examiner has misapplied the test for interpreting unexpected results. At page 3 of the Office Action, the Examiner asserts that “[a]pplicant and declaration refer to VLPs of Latham *et al.* The rejection is based on two references and the

obviousness to combine..." The Examiner further argues "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Applicants submit that they are not attacking references individually. Rather, Applicants have simply compared the claimed invention with the closest prior art (Latham *et al.*). As stated in the MPEP at 716.02(e), when showing unexpected results, the "applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." (emphasis added). Moreover, "requiring applicant to compare [the] claimed invention...suggested by the combination of references relied upon in the rejection...'would be requiring comparison of the results of the invention with the results of the invention.'" MPEP 716.02(e), citing *In re Chapman*, 357 F.2d 418, 422. Accordingly, by showing significant and practical unexpected results compared to the closest prior art, Applicants have done everything required of them to rebut the purported *prima facie* case of obviousness and thus the rejections must be withdrawn.

Written Description Rejections Under 35 U.S.C. 112, 1st Paragraph

Claims 64-65 have been rejected under 35 U.S.C. 112, first paragraph. While Applicants dispute the underlying reasons for the rejection, they will cancel claims 64-65 without prejudice pending a decision from the pre-appeal brief conference, thus rendering the rejection moot.

SUMMARY

Applicants respectfully submit that the rejections of record are clearly improper and request that the rejections be withdrawn. Applicants respectfully request such a finding for the reasons set forth herein. The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper.

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